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Invited review

Allergy and risk of hematologic malignancies: Associations and mechanisms

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ABSTRACT

Increasing evidence indicates that a dysregulated immune system, as the one found in allergic disorders, can affect survival of tumor cells. A possible association between allergies and risk of hematologic malignancies has been examined in several epidemiological studies; however, results were not always consistent.

The aim of this review is to report the preclinical and clinical data, which support a correlation between allergy and hematologic neoplasms.

Immune system modulation could represent a powerful tool in the prevention and treatment of hematologic malignancies.

Contents

1. Introduction

Allergic diseases require sensitization of a predisposed individual to a specific antigen. Exposure of a susceptible individual to an allergen results in its processing by antigen presenting cells (APC), including macrophages and dendritic cells (DC) located throughout the body surfaces in contact the outside environment, such as nose, lungs, eyes, skin, and intestine. These APCs process the allergen protein and present the epitope bearing peptides via their MHC to particular T cell subsets. T cell responses depend on both cognate recognition through various ligand/receptor interactions and on the cytokine micro-environment, with IL-4 directing a T helper (Th)2 response and interferon (IFN)γ a Th1 profile.

Peripheral T cell tolerance to environmental antigens is crucial for a healthy immune response and no allergy. The balance between Th2 cells and T regulatory (Treg) cells has a critical role in the generation of immune responses to environmental antigens. Allergic individuals display an aberrant activation and expansion of Th2 cells. It appears that aberrant activation of Th2 cells in allergy is secondary to impaired mechanisms of peripheral T cell tolerance that is normally mediated by antigen-specific T cell anergy, Treg cells, and suppressive cytokines, IL-10 and TGF-β [1].

However, increasing evidence indicates that dysregulation of the immune system, as the one found in allergic dysregulation, can affect survival of tumor cells. [2].

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The aim of this review is to report the preclinical and clinical data, which support a correlation between allergy and hematologic neoplasms.

2. Allergy and hematologic malignancies

The majority of studies reported in literature have explored the relationship between allergy and lymphoma or acute lymphoblastic leukemia. In fact, it is only for these diseases that the strongest correlations with the allergic state have been detected, while for the other hematological diseases reports are sporadic and sometimes anecdotal.

A possible association between allergies and risk of hematologic malignancies (HM) has been examined in several epidemiological studies; however, results were not always consistent [3].

In contrast, inverse associations were reported mainly in case-control design studies. There have been several investigations regarding definition and measurement of allergies and the subtypes of HM assessed, however, an inverse association with history of allergies has been reported for HM as a group [4], lymphoma overall [5,6], Hodgkin's lymphoma (HL), Non Hodgkin lymphoma (NHL)[7–10], Acute Lymphoblastic Leukemia (ALL) [11,12], and multiple myeloma (MM)[13] (Table 1).

Shadman et al. used the Vitamins and Lifestyle (VITAL) cohort to examine the association between allergies and risk of hematologic malignancies. From 2000 to 2002, 66,212 participants, aged 50–76, completed a baseline questionnaire on cancer risk factors, medical conditions, allergies, and asthma. Through 2009, incident HMs (n5681) were identified via linkage to the Surveillance, Epidemiology, and End Results Cancer Registry.

After adjustment for factors possibly associated with HMs, a history of airborne allergy was associated with increased risk of HMs (hazard ratio [HR] = 1.19 [95% confidence interval: 1.01–1.41], $P = 0.039$) in Cox proportional hazards models. This association was limited to allergies to plants/grass/trees (HR = 1.26 [1.05–1.50], $P = 0.011$) and was strongest for some mature B-celllymphomas (HR = 1.50 [1.14–2.00], $P = 0.005$). Gender-stratified analyses revealed that the associations between airborne allergies overall and those to plants, grass, and trees were only seen in women (HR = 1.47 [1.14–1.91], $P = 0.004$; and HR = 1.73 [1.32–2.25], $P < 0.001$) but not men (HR = 1.03 [0.82–1.29], $P = 0.782$; and HR = 0.99 [0.77–1.27], $P = 0.960$) [14]. The study indicates a moderately increased risk of HMs in women but not in men with a history of allergies to airborne allergens, especially to plants, grass, or trees. However, this association was not uniform across all the subtypes of HM, rather it was primarily found in some mature B-cell neoplasms.

Several other studies have attempted to ascertain the risk of acute and chronic lymphoid malignancies in patients suffering from allergic diseases. In a US veterans study, a history of "total allergic conditions" as documented in the hospital records was associated with a diagnosis of NHL (risk ratio [RR] = 1.4 [1.3–1.5]). Significant associations were also observed with specific allergic conditions such as alveolitis, dermatitis, and erythema, but not asthma [15].

Other studies indicate a positive association, especially for Hodgkin Lymphoma (HL) [16,17] or no effect [18].

Moreover, in a population-based study from the Swedish cancer registries, an increased risk of lymphoplasmacytic lymphoma was reported in patients who had a history of "any type of allergy or chronic inflammatory conditions" based on previous hospital discharge information (RR = 1.2 [1.0–1.4]) [19].

Different works have shown a correlation between specific allergic diseases and hematological malignancies. In a Swedish cohort of more than 16,000 twins, the risk of leukemia was higher in patients with self-reported history of hives (RR = 2.1 [1.0–4.5]) while no association was found between different subtypes of allergies and incidence of leukemia, CLL, NHL or MM [20]

However, when evaluating risk of acute childhood leukemia in allergic patients, Chang et al. [21] utilized a population-based case-control design using medical claims data from the National Health Insurance Research Database of Taiwan. Eight hundred forty-six childhood ALL patients who were newly diagnosed during 2000 to 2008 and were older than 1 but less than 10 years of age were individually matched with 3374 controls based on sex, age, and time at diagnosis (reference date for the controls). Conditional logistic regression was performed to assess the association between childhood ALL and allergies. An increased risk of ALL was observed in those with allergy less than 1 year before ALL diagnosis (odds ratio (OR) = 1.7, 95% CI: 1.5, 2.0), more than 1 year allergy before ALL diagnosis (OR = 1.3, 95% CI: 1.1, 1.5), and before 1 year of age (OR = 1.4, 95% CI: 1.1, 1.7).

In this study, childhood ALL was positively associated with subject having allergies before 1 year of age less than 1 year before diagnosis, and more than 1 year before diagnosis.

Association between childhood ALL and allergies is contrary to the results of most previous studies. The inconsistency can partly be explained by the sources of exposure data (medical records *vs.* parental report), participation rate, and exposure latency.

Moreover, Nunez-Enriquez et al. conducted a multi institutional population-based case-control study on children with Down syndrome and found that asthma was a risk factor for development of acute leukemia (OR = 4.18 and 95% CI: 1.47–11.87) while, other allergies had no effect or were protective [22].

The intrinsic immune dysregulation that was well described in children with Down syndrome, likely had a significant role in the association between allergic phenomena and ALL [23].

However, Down syndrome might be a confounder in the relation between asthma and acute leukemia. Altogether, Down syndrome may be considered as the cause for both asthma and acute leukemia thus drawing a causative link between asthma and acute leukemia in this setting could be a raw conclusion [24].

Nonetheless, similar results were also reported by other authors. In fact, several papers suggest that asthma is a risk factor for AL in children with DS, whereas skin allergies seemed to protect the population from AL. Children with DS are more vulnerable to the effects of environmental factors that have been associated with the development of AL [25,26].

Finally, children born to mothers with allergies are more likely to have impairment of Tregs cells [27] and a decreased ability to respond to microbial challenges [28]. Similarly, higher maternal serum immunoglobulin E, an indicator of maternal allergy status, was associated with a higher risk of childhood ALL [29].

However, while prospective cohort studies suggested an increased risk of HM, case-control studies failed to confirm these findings, rather they have shown an inverse relationship [30].

In fact, it has been proposed that allergies influence the development of childhood leukemia. Different studies have been conducted in this field; however, their results are not conclusive, as several works have concluded that allergies are risk factors or protective factors [31–34].

Moreover, beyond this inverse association of allergic history with childhood ALL, a similar association is highlighted when serologic markers of allergic predisposition are used as an alternative measure of allergy.

In a study conducted on 252 cases of childhood (0–14 years) ALL, newly diagnosed allergen-specific IgEs, as markers of allergic predisposition, against 24 of the most prevalent respiratory and food allergens, were determined, using an enzyme immunoassay procedure for 199 children with ALL and 113 controls. Cases were compared with controls through frequency distributions and unconditional multiple logistic regression models to estimate ORs

Table 1
Summary of studies on allergy and risk of hematologic neoplasms.

First author/year	Reference number	Type of allergy	Type of HM	Statistics
Shadman M/2013	[14]	Air born allergy (plants/grass/trees)	HM mature B-cell lymphomas	HR = 1.19 [95% CI: 1.01–1.41], $P = 0.039$ HR = 1.50 [1.14–2.00], $P = 0.005$
Koshiol J/2011	[15]	Total allergic conditions	NHL	[RR] = 1.4 [1.3–1.5]
Kristinsson SY/2010	[19]	Any allergy or chronic inflammatory conditions	Lymphoplasmacytic lymphoma	RR = 1.2 [1.0–1.4]
Soderberg KC/2004	[20]	Hives	Leukemia	RR = 2.1 [1.0–4.5]
Chang JS/2011	[21]	Not specified	ALL	OR = 1.7, 95% CI: 1.5, 2.0, less than 1 year before the case's ALL diagnosis OR = 1.3, 95% CI: 1.1, 1.5, more than 1 year before the case's diagnosis OR = 1.4, 95% CI: 1.1, 1.7, before the age of 1 year
Nunez-Enriquez JC/2013	[22]	Asthma	Acute leukemia	OR = 4.18 and 95% CI: 1.47–11.87
Lariou MS 2013	[35]	Self-reported-allergic history Serum specific IgE Food IgE	ALL	OR = 0.49, 95% CI: 0.34-0.72 OR = 0.43, 95% CI: 0.22-0.84) OR = 0.39, 95% CI: 0.18-0.83
Dikalioti SK/2012	[36]	Not specified asthma	NHL	OR = 0.50, 95% CI: 0.27–0.92 OR = 0.43, 95% CI: 0.21–0.88
Landgren O/2006	[38]	Not specified	MM	OR = 0.4; 95% CI: 0.3–0.7

HM: hematological malignances; NHL: non Hodgkin lymphoma; ALL: acute lymphoblastic leukemia; MM: multiple myeloma; HR: hazard ratio; CI: confidence interval; RR: risk ratio; OR: odds ratio.

and 95% (CIs) regarding associations of allergy with childhood ALL.

Self-reported-allergic history (OR = 0.49, 95% CI: 0.34–0.72) and practically every one of its main components (respiratory, food, any other clinical allergy) were strongly and inversely associated with ALL. Likewise, the serum IgE inverse association was of the same magnitude (OR = 0.43, 95% CI: 0.22–0.84) mainly due to food IgE (OR = 0.39, 95% CI: 0.18–0.83) [35].

There is a similar discrepancy between works reported in literature on lymphoma. Furthermore, the papers appear to highlight the direct correlation between allergy and chronic lymphoproliferative dysregulations while other papers seem to light the protective effect.

Between 1996 and 2008, 277 children (aged 0–14 years) with HL ($N = 111$) or NHL ($N = 166$) were enrolled in Nationwide Registry for Childhood Hematological Malignancies (NARECHEM), from a Greek hospital-based registry of childhood hematological malignancies. Hospital controls were individually matched to cases on age and sex. Multivariate conditional logistic regression was used to estimate ORs with 95% CIs for associations of allergic diseases and other covariates with childhood HL or NHL risk. Subsequently, the authors combined their results with those of a French case-control study in a meta-analysis counting a total of 330 NHL cases/1478 controls and 239 HL cases/959 controls. After investigating on sociodemographic, perinatal and environmental factors, childhood NHL was less prevalent among children with allergy associated symptoms (OR = 0.50, 95% CI: 0.27–0.92) or a history of asthma (OR = 0.43, 95% CI: 0.21–0.88). By contrast, allergy did not seem to be associated with childhood HL risk, although statistical power was limited. However, fewer seaside holidays and higher birth weight were also associated with increased childhood NHL risk. The combined OR of the two studies for the association of asthma with NHL risk was: 0.52, 95% CI: 0.32–0.84, whereas for HL: 0.86, 95% CI: 0.51–1.45. Thus, allergy seemed to be strongly and inversely associated with childhood NHL [36].

A powerful pooled analysis of adulthood NHL also showed an apparent protective effect of asthma, hay fever and allergy against B-cell NHL [37].

Finally, a reduced MM risk was found among women who had a medical history of allergy (OR = 0.4; 95% CI: 0.3–0.7). However, this study shows conflicting results because certain conditions (such as allergy, bronchitis, psoriasis, and eczema) were associated with reduced risk of MM, whereas others (such as asthma and hay fever) were not associated with multiple myeloma risk [38].

3. Allergy as risk factor: possible mechanisms

Various explanations have been proposed to account for the observed increased incidence of HM in patients with immune dysregulation. Relevant factors could be genetic and environmental risk factors, chronic activation and replication of lymphocytes and the subsequent increased chance of mutations, and finally epigenetic changes, for example, via effects on antigen recognition by T cells [39].

Effects of the treatments used by patients with allergies on the cancer risk do not seem to explain the association, as associations between uses of antihistamines, leukotriene agonists, or other common therapeutic agents for allergies with HM have not been reported.

The association between allergy and childhood ALL suggests that the two diseases may have a common biologic mechanism.

Two paradigms, "missing immune deviation" and "reduced immune suppression," have been proposed to explain the biologic basis of this hypothesis [40]. Moreover, in order to explain the role of allergies as a risk factor for cancer, it is worth considering the antigenic stimulation hypothesis which proposes that chronic stimulation of the immune system will provoke randomly occurring pro-oncogenic mutations in actively dividing cells [20].

For instance, chronic lymphocytic leukemia (CLL) is a tumor of circulating B cells, variably stimulated and anergized following exposure to antigen in lymphoid tissues [41].

The hyper reactivity of the B-cell receptor (BCR) to unknown antigen ligation plays a pivotal role in CLL cell survival. Several authors aimed to investigate the BCR signaling pathway using proteomics to identify novel proteins which may have clinical relevance in this disease [42].

Almost 30% of CLL patients share BCRs with restricted, quasi-identical "stereotyped" immunoglobulin (IG) sequences with highly homologous IG variable heavy-chain complementarity-determining region 3 (VH CDR3), the key determinant of antigen specificity. This finding, along with other structurally unique features of CLL BCRs, strongly suggest that antigens, superantigens or both may play an active role in the disease [43]. The latter strongly supports a role for persistent antigen stimulation in the clonal evolution of CLL [44].

A different lymphoprolipherative disease with the same pathogenesis could be the Large Granular Lymphocyte (LGL) leukemia. LGL leukemia represents a rare chronic lymphoproliferative dysregulation of CTLs, a malignancy that involves lymphocyte

infiltration of multiple organs, including the BM, liver, and spleen. Phenotypically, LGL leukemia can arise from either $CD3^+$ CTLs or $CD3^-$ NK cells. The World Health Organization (WHO) classification includes T-cell LGL leukemia in the subgroup of mature peripheral T-cell neoplasms and distinguishes it from aggressive NK-cell leukemia [45].

LGL leukemia is thought to arise from chronic antigenic stimulation, with the long-term survival of LGL being promoted by constitutive activation of multiple survival signaling pathways [46].

During infection exposure or Ag stimulation, LGLs undergo vigorous proliferation by approximately 50,000-fold upon priming by target cells, and at a later time after Ag clearance, are selectively eliminated by a process called activation induced cell death (AICD). However, in LGL leukemia patients, the AICD process is dysfunctional and activated CTL cells do not undergo apoptosis efficiently, leading to an elevated number of LGLs in the peripheral blood. Multiple cell survival pathways, including JAK2/STAT3, sphingolipid signaling, RAS/MEK/ERK, and SFK/PI3K/Akt, have been found to be constitutively activated in LGL leukemia patients. A system biology approach identified IL-15 and PDGF as master survival signaling switches that may have a deep effect on all known deregulations in T-LGL leukemia [47–55].

An interesting datum could be that the treatment of leukemic LGL is based on immunosuppressive therapy, primarily using low doses of methotrexate or cyclophosphamide.

Associations between multiple myeloma and past history of disorders characterized by chronic immune dysfunction and/or antigen stimulation have also been suggested in epidemiological studies; however, there are inconsistencies in the literature on this topic [56–59].

Antigenic targets of monoclonal gammopathy of undetermined significance (MGUS) and multiple myeloma (MM) paraproteins have been suggested to play an important role as growth stimulators in the pathogenesis of these neoplasms. To identify such targets, Preuss et al. screened cDNA libraries from human testis, lung and breast cancer, bovine and porcine muscle and wheat germ for reactivity with paraproteins in the sera from 115 patients with MGUS and MM. Of $>6 \times 10(8)$ paraprotein–antigen interactions screened, an IgA paraprotein from a female patient bound to sperm-specific cylicin-2, and 3 IgG paraproteins bound to tripeptidyl-peptidase-II (TPP-2), insulin-like growth-factor binding-protein-2 (IGFBP-2) and porcine kinesin. Specificity was confirmed by reverse Western blots using recombinant antigens. The broad spectrum of auto-, allo- and heteroantigens as targets of human paraproteins in patients without signs of chronic antigenic stimulation renders a causal role of the antigenic stimulus in the pathogenesis of MGUS and MM as unlikely [60].

The importance of clinical or subclinical immune dysregulation in development of HM in cases occurring in the general population, who comprise the majority of cases, is unclear. However, in allergic individuals, antigenic stimulation subjects the immune system to a chronically hyper reactive state, leading to an inflammatory cascade of cellular and cytokine reactions that tax the host immune response, provoke tissue injury, and eventually result in lymphoid neoplasia [61].

Thus, a B-cell stimulatory host environment increases the risk of B-cell NHL among immuno-competent persons, and a modified pattern of cytokines production could be relevant in the onset of HM.

IL-12 is important for normal immune development that shifts the immune profile from T-helper 2 dominant among newborns to T-helper 1 dominant with increasing age [62]. The absence of this shift and the presence of a T-helper 2-dominant immune profile are associated with an increased risk of allergy, but IL-12 also appears important for childhood ALL. In fact, a previous study reported that the variant G allele of the single nucleotide polymorphism rs583911 of the interleukin 12A gene, which codes for a part of IL-12 cytokine, is associated with an increased risk of childhood ALL [63].

Moreover, although IL-10 can be produced by many cell types, it is produced by a type of T-regulatory cell known as T-regulatory 1 at particularly high levels to suppress overactive immune reaction [64], and a recent study showed that children with ALL had lower IL-10 level at birth than did healthy children [65], while cord blood samples of children with allergy have exhibited a lower immune response of the T regulatory 1-related cytokine IL-10 compared with healthy children [66,67].

Finally, increased serum/plasma levels of molecules involved in B-cell activation, including soluble sCD23, sCD27, sCD30, sCD44, and CXCL13, have been associated with subsequent development of AIDS-related NHL. B-cell activation is characterized by lymphocyte proliferation, class switch recombination, and somatic hypermutation, all of which are prone to resultant errors in DNA that may lead to lymphomagenesis [68–71].

A different hypothesis could explain the correlation between allergy and HM.

Although the definite causes of childhood leukemia are still largely unknown, it is believed that a lack of "priming" by infections during early childhood may cause a dysregulated immune response to infections later in childhood, leading to the development of childhood leukemia, particularly acute lymphoblastic leukemia (ALL) (Greaves' "delayed infection" hypothesis) [72]. Moreover the underlying biologic mechanism in the delayed infection hypothesis is also applicable to the hygiene hypothesis proposed by Strachan to explain the rising prevalence of allergy in the Western population [73].

Given the similarities between the delayed infection hypothesis of childhood leukemia and the hygiene hypothesis of allergy, it is counterintuitive that in the majority of studies, an inverse association between allergy and childhood leukemia (mostly childhood ALL) [12,31,33,34,74–78] was observed with only one exception [32].

An overactive and dysregulated immune reaction in response to pathogens may lead to the expansion of a preleukemic clone, resulting in the occurrence of additional mutations and the development of childhood leukemia [72].

4. Allergy as protective factor: possible mechanisms

In comparison, allergies as protective factors can be explained in terms of the immune-surveillance hypothesis, which suggest that allergic diseases enhance the immune system's ability to detect and eliminate neoplastic cells.

The immune system has the ability to recognize and eliminate nascent transformed cells in the body, thus preventing a majority of potential cancers from developing. The presence of an allergic condition could be a surrogate marker of increased vigilance of the immune system in scrutinizing, identifying, and destroying cancer cells [11].

In allergic subjects, there is bone marrow involvement with reprogramming of bone marrow stem cells, regarded as 'reflex" nature of allergic disease. Allergic phenotype in an atopic child may lead to epigenetic reprogramming that in turn affects immune surveillance by increasing antigen-presenting cell activity [79]. Hence, it seems that increased surveillance by hyperactive immune system of allergic patients is a reality.

Another is the adrenal hypothesis, which proposes that infections produce changes in the hypothalamus-pituitary-adrenal axis and subsequently an elevation in plasmatic cortisol, provoking the elimination of leukemic and preleukemic cells. This mechanism is possible under allergic conditions because the drugs commonly

used to treat allergies include corticosteroids, which could provide the same protective effect against the development of AL that early infections provide [80].

A less plausible explanation could point to the antitumor activity of histamine [81], a chemical mediator of allergic reactions that protects natural killer cells and T cells against oxygen radical-induced damage and death by suppressing oxygen radical formation, and also optimizes lymphocyte activation by cytokines [82]. Clinical trials in malignancies such as metastatic malignant melanoma and acute myeloid leukemia have demonstrated that histamine dihydrochloride in combination with immunotherapy has the potential to improve treatment outcome, further supporting the posssible antitumor effect of histamine [83,84].

On the other side, it has already been demonstrated that histamine may play a role in mycosis fungoides, particularly in advanced stages of the disease. Histamines, but also other mediators released by mast cells, are not only associated with pruritus, but may have tumor growth promotion and immune-regulating properties [85,86].

The antihistamines clemastine and desloratadine can possess immune suppressive or regulatory properties including inhibition of antigen-specific as well as mitogen-induced lymphocytes proliferation. These properties were independent on histamine-1-receptor expression, but dependent on extracellular signal regulated kinase (ERK)-dependent proinflammatory cytokines such as TNF-a and IL-6 [87,88].

Döbbeling et al. evaluated the effect of clinically approved antihistamines on the growth of CTCL cell lines. CTCL cell lines as well as blood lymphocytes from patients with Sézary syndrome were cultured with antihistamines, and the cells were analyzed for proliferation, apoptosis, and expression of programmed death molecules and transcription factors. The two antihistamines clemastine and desloratadine, induced potent reduction of the activities of the constitutively active transcription factors c-Myc, STAT3, STAT5a and STAT5b in mycosis fungoides and Sézary syndrome cell lines. This inhibition was followed by apoptosis and cell death, especially in the Sézary syndrome-derived cell line Hut78 that also showed increased expression of the programmed death-1 (PD-1) after clemastine treatment. In lymphocytes isolated from Sézary syndrome patients, the CD4-positive fraction underwent apoptosis after clemastine treatment, while CD4-negative lymphocytes were hardly affected [89].

There are more things in heaven and hearth . . .

5. Allergy, sex and solid neoplastic diseases

Recent studies have demonstrated that serum eosinophil count is inversely associated with colorectal cancer development, and a history of allergy decreases the risk of pancreatic cancer [90,91], while atopic exposures may be protective against childhood rhabdomyosarcoma (RMS). In a case-control study of 322 childhood RMS cases and 322 pair-matched controls Lupo et al. assessed the following atopic conditions were assessed: allergies, asthma, eczema, and hives. As the two most common histologic types of RMS are embryonal ($n = 215$) and alveolar ($n = 66$), they evaluated effect heterogeneity of these exposures. Allergies (OR = 0.60, 95% CI: 0.41–0.87), and hives (OR = 0.61, 95% CI: 0.38–0.97) were inversely associated with childhood RMS. These exposures did not display significant effect heterogeneity between histologic types. This is the first study indicating that atopic exposures may be protective against childhood RMS, suggesting additional studies are needed to evaluate the immune system's role in the development of this tumor [92]

Thus, the relationship between allergy and solid neoplastic diseases also appears to be an important field of investigation.

However, a different and interesting field of research is the different influence of sex on the risk of HM in allergic patients. In fact, gender differences are reported in the association between history of allergies and cancer. It is tempting to speculate that the additional effect of allergy may reach statistical significance in women because of their lower baseline risk for the development of HM compared to men. However, hormonal effects on the (dysregulated) immune system and interactions with carcinogenesis may offer an alternative biological explanation that will required further mechanistic studies.

6. Conclusions and future perspectives

In the future, many other factors should be studied to investigate the relationship between allergies and cancer, such as the influence of tumors on the possible manifestation of allergy symptoms. We have to consider that individuals with pre-clinical NHL experience immune suppression that leads to the reduction of allergic symptoms [8].

However, after we have reviewed the most recent literature on the relationship between allergy and cancer, we must try to justify the discrepancies that exist and the different conclusions reached by various authors. It is probable that different immunological alterations that accompany different allergies, may affect tumor susceptibility in a completely different way.

In both allergy and cancer biology, for example, antibodies may be beneficial or detrimental, depending on their epitope specificity [93,94]. In allergy, specific immunotherapy (SIT) with allergens aims to induce antibodies which block, but do not enhance the allergic reaction. Similarly, in immunological targeting of antigens overexpressed by malignant cells, growth-inhibitory antibodies are preferred, whereas growth-stimulating specificities should be prevented. Therefore, in both cases it is important to direct immune responses to inhibitory antibody epitopes of the allergen/antigen [95].

The importance of antibodies in activating immune responses against tumors is now better appreciated with the emergence of checkpoint blockade antibodies and with engineered antibody Fc domains featuring enhanced capacity to focus potent effector cells against cancer cells. Antibodies designed with Fc regions of the IgE class can confer natural, potent, long-lived immune surveillance in tissues through tenacious engagement of high-affinity cognate Fc receptors on distinct, often tumor-resident immune effector cells, and through ability to activate these cells under tumor-induced Th2-biased conditions. IgE is a novel anti-cancer modality, and several IgE-based active and passive immunotherapeutic approaches have been tried in different *in vitro* and *in vivo* model systems, collectively suggesting the potential of IgE immunotherapies in oncology [96].

The assumption on an inverse association between allergy and IgE levels and cancer derives from epidemiological data [97]. IgE antibodies directed against a tumor-associated antigen could specifically trigger an immediate local effector cell response against the tumor cells [98]

Engineered anti-tumor IgE antibodies have a high cytotoxic capacity due to interaction with potent effector cells. However, natural IgE has also been described in squamous cell carcinoma of the head and neck [99] and in pancreatic cancer where its cytotoxic potential was also demonstrated [100]. The mechanisms of anti-tumor IgEs have already been studied in detail in several previous experiments, among them ADCC and antibody-dependent cell-mediated phagocytosis (ADCP) seem to be most important [101–103].

However, although several studies suggest an increased risk of HM in patients with reported history of allergies, this association

was not uniform across all the subtypes of HM and it has be denied in several works.

In this regard it should be remembered that even though we have listed several studies on the association between allergies and hematological malignancies, a vast majority of these studies are epidemiological studies. Although the contribution of epidemiologic methods in elucidating the determinants and etiological factors in human disease has a long history, some practical limitations of epidemiologic methods have to be highlighted.

There are two main limitations to epidemiological studies: the first is statistical and gives rise to random errors; the other concerns demography and gives rise to systematic errors. Groups of at least several thousand people would need to be followed throughout their lives in order to identify a statistically significant excess of cancer between two populations. The second limitation results from the need to match the study and control groups for any confounding factors that may influence the incidence of cancer. Unless the study and control groups are drawn from a single homogeneous population, it is rarely possible to match the groups, or to make allowances for the differences, with sufficient accuracy to detect, with confidence, a small increase in cancer mortality. Any inadequacy in the matching may give rise to a bias that cannot be reduced merely by expanding the size of the groups [104].

Despite these limitations, epidemiologic studies have been remarkably productive in elucidating etiological factors.

In conclusion, several studies provide empirical evidence that allergic disorders are associated with a direct or inverse risk of developing hematologic malignancies.

In fact, a dysregulation of the immune system might have both positive and negative influence on the occurrence of cancer. The presence of an allergic condition could be a surrogate marker of increased vigilance of the immune system in scanning for, identifying and destroying cancer cells. On the other hand, in allergic individuals, antigenic stimulation subjects the immune system to a chronically hyper reactive state, leading to an inflammatory cascade of cellular and cytokine reactions that provoke tissue injury and eventually result in neoplasia.

It is therefore certain that there is a clear specificity between alteration of the immune system and the onset of hematologic malignancies. The cell type concerned, myeloid or lymphoid, age, sex, and comorbidities seem able to change the type of influence exerted by the immune system. Therefore, generalizations about the influence of the immune system on hematologic malignancies appear unnecessary and misleading.

Further studies should assess the real impact of allergies on any specific hematological disease.

Epidemiological studies that include the evaluation of different immunological effectors will be needed for a confirmation of this association and to explain the intimate mechanisms that underlie the increased susceptibility or the protective effect exerted by allergy on neoplastic diseases.

Conflict of interest statement

The authors declare no conflict of interest.

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